Exhibit A

FINAL

Opinion on the Relationship between Ovarian Cancer and Cosmetic Talc Powder Use:

Causality and Relevance to the Case of Ms. Deane Berg

Civil Action Number 4:09-CV-04179-KES

An Opinion Prepared for:

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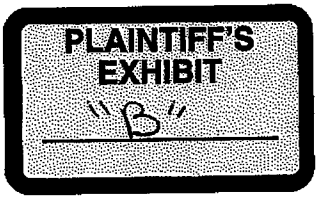


Introduction

The following is my review of the epidemiologic data regarding the association between use of cosmetic talc powders in the genital area and ovarian cancer with regard to the likelihood that this is cause-and-effect. I will also comment on the possible relevance of talc use to the occurrence of ovarian cancer in the specific case of Ms. Deane Berg who has indicated that she used talc on a daily basis as a dusting powder to her genital area for more than 30 years. I have divided this report into the following sections: Historical Material, Epidemiologic Studies, Meta-Analyses, Causality, Agency Opinions, and Relevance of Talc in the Berg Case. I reserve the right to update this report based on new epidemiologic data or material to be revealed at deposition or discovery.

Historical Material

There are a number of studies done prior to 1980 which are important because they provided the foundation for the hypothesis linking talc and ovarian cancer. A study by the Grahams in 1967 [1] highlighted the similarity of ovarian cancer and mesothelioma (a type of cancer caused by asbestos), showed that (intraperitoneal) injection of asbestos into the abdominal cavity of rabbits and guinea pigs induced epithelial changes (papillary proliferation) in surface ovarian cells similar to those they had observed in women with early ovarian cancer, and found clusters (foci) of inflammatory cells (histiocytes) with birefringent crystals in 6 of 12 ovaries from women with borderline or invasive ovarian cancer but none in 9 normal ovaries. In this report, the Grahams cited a case series describing abdominal neoplasms and ovarian cancer in women with asbestosis of the lung [2]. A subsequent occupational study confirmed a greater risk for ovarian cancer in women with exposure to asbestos [3]. Concluding notable studies done prior to 1970, Cralley et al [4] described variable amounts of asbestos contamination of cosmetic talc powders as well as trace metals such as nickel and chromium—findings confirmed in a subsequent report by Rohl [5].

The first study to suggest a possible link between ovarian cancer and talc was a report by Henderson et al. in Cardiff, Wales describing talc particles "deeply embedded" in 10 of 13 ovarian tumors, 12 of 21 cervical tumors, one primary carcinoma of the endometrium, and 5 of 12 "normal" ovaries from women with breast cancer [6]. Although the authors of this report acknowledged limitations of their study, the article generated commentaries and debate that would be chronicled in the well-known British Journal, Lancet, during the late 1970's.

In 1977, the Lancet published an (anonymously-written) editorial [7] regarding talc which reviewed data on inhaled talc and concluded that "it seems unlikely that future exposure to cosmetic talc of the specifications now agreed to by major manufactures will present a health hazard." The Editorial also stated that early skepticism about the Henderson report was "well-founded" since there had been no confirmatory evidence provided in the 6 years since Henderson's report. Following this editorial, a letter to Lancet was published in 1979 from Henderson's group [8] in which they cited additional studies (e.g. [9]) which had, in fact, been performed subsequent to the 1971 article and which they said supported their contention that the particles found were talc.

Also in 1979, after the Henderson letter, a commentary on talc and ovarian cancer [10] appeared in Lancet entitled "Cosmetic Talc and Ovarian Cancer." This article was authored by Daniel L. Longo who went on to become Director of the National Institute of

Aging and Robert C. Young who became President of Fox Chase Cancer Center. They presented no new data but reviewed current evidence and concluded that: "Epidemiological, experimental, and clinical data seem to link asbestos and talc with ovarian cancer. Direct passage of talc or asbestos-contaminated talc to the ovarian surface may play an aetiologic role. Further systematic evaluation of talc and asbestos as ovarian carcinogens is needed." Lancet then published a letter responding to the Longo and Young commentary from Francis J.V.C. Roe, a consultant to the Cosmetic, Toiletry, and Perfumery Association [11], who stated that further research on the biologic effects of talc and significance of mineral particles in tissues "merits little priority." Longo and Young responded [12] that they found it disturbing that a consultant to the cosmetic industry would take that stand.

Despite the debate and discussion about talc and ovarian cancer in the U.K. from 1970 to 1980, no formal epidemiologic study addressing the association was performed during that period. The occupational epidemiologist, Muriel Newhouse, published a case-control study of ovarian cancer in 1977 [13] but did not mention the association in the paper. Newhouse also wrote a letter to Lancet [14] that was critical of Longo and Young for failing to reconcile the talc and ovarian cancer hypothesis with other risk factors she had observed in her study that increased ovarian cancer risk including fewer pregnancies, less oral contraceptive use, and lower occurrence of childhood mumps.

Epidemiologic Data

It would not be feasible (and obviously not ethical since we envision a potentially harmful effect) to construct a study involving randomization of women to long term talc use or no use and follow them for decades to determine who got ovarian cancer. Thus human data to support an association between talc and ovarian cancer must come from epidemiologic studies of two types—case-control or cohort studies. In a case-control study, case women with ovarian cancer are queried about talc use (before they developed ovarian cancer) and, similarly, controls without ovarian cancer are questioned about their talc use. Inferences about a relationship between talc use and ovarian cancer are derived by comparing the odds or likelihood that cases were exposed or not exposed to talc compared to the odds that controls were exposed or not exposed. In a cohort study, women who do not have ovarian cancer are identified and each characterized by whether she is or is not being exposed to talc through personal habits or occupation. The cohort is followed over time to determine how frequently ovarian cancer occurred in the exposed compared to the non-exposed group. If relatively more cases than controls reported exposure to talc in a case-control study or relatively more women exposed to talc in a cohort study developed ovarian cancer compared to non-exposed, then these observations would suggest talc use may be associated with greater risk for ovarian cancer.

The measure used to characterize risk is commonly called the odds ratio (OR) in a case-control study or relative risk (RR) in cohort study, although RR is frequently used in place of OR. An OR or RR greater than 1 (the "null" value indicating no association) indicates the exposure may increase risk for disease. The greater the deviation from 1, the stronger the association is considered. Statistical tests (yielding a "p value") are performed to determine whether chance may explain the deviation from 1. P values less than 5% are considered significant and less likely to be due to chance. A 95% confidence interval is constructed around the OR (or RR) estimate in which we expect the true measure of the association to lie based upon sampling statistics. A lower

confidence limit above 1 indicates that the exposure significantly increases risk, while an upper confidence bound less than 1 indicates that the exposure significantly decreases risk. ORs or RRs are described as "adjusted" if factors (possible confounders) that are thought may influence risk for disease or likelihood of exposure are taken into consideration and "crude" if they are not.

The first epidemiologic study performed on cosmetic talc powder use in the genital area and ovarian cancer was a case-control study performed by me and colleagues [15]. In this study, 215 women with epithelial ovarian cancer and 215 age matched controls selected from the general population were questioned about their talc use (prior to developing ovarian cancer in cases). 42.8% of cases reported regular use of talc powders either as a body dusting powder to the perineum or use on underwear or sanitary napkins compared to 28.4% of controls. This translated into a significant OR (and 95% confidence limits) of 1.92 (1.27, 2.89) for ovarian cancer associated with talc use. The association was significant after adjustment for parity and menopausal status. After this publication, I was contacted by Dr. Bruce Semple of Johnson and Johnson and we met in Boston in late 1982 or early 1983. My recollection of this meeting was that Dr. Semple spent his time trying to convince me that talc use was a harmless habit, while I spent my time trying to persuade him to consider the possibility that my study could be correct and that women should be advised of this potential risk of talc. I don't recall further meetings or communications with him.

Since 7/1982 when my paper was published through 12/2010, I am aware of 21 additional papers which have provided epidemiologic data addressing the talc and ovarian cancer association [16-36] (Attachment 1). These include 19 case-control studies, 1 cohort study [32], and 1 study combining case-control and cohort data [34]. Nearly all of these studies have reported an elevated risk for ovarian cancer associated with genital talc use and the majority statistically significant elevations.

Meta-Analyses

Meta-analysis is a statistical technique that allows similar measures of the same illness and exposure (or treatment and effect) from different studies to be combined so that a more powerful test can be performed about whether there is an association. A meta-analysis also provides a summary odds ratio or relative risk that is a more precise estimate of the overall effect (i.e. smaller 95% confidence interval). The investigator also does a "test for heterogeneity" (also called a test for homogeneity) in which s/he seeks to determine whether the odds ratios differ to such a degree that it suggests the studies may not have been conducted similarly.

I am aware of five meta-analyses which have been performed on the topic of talc and ovarian cancer. All five of these, including two which were industry-sponsored, found a significant positive association between the use of talc and ovarian cancer. The first meta-analyses was conducted by Harlow and Cramer from our second study of ovarian cancer [20] which included the odds ratio from a new series of 235 cases with ovarian cancer and 239 controls and 5 other published studies [15-19]. The summary OR (and 95% confidence interval) was 1.3 (1.1, 1.6) indicating a significant overall association. The conclusion from this study was that "a lifetime pattern of talc use may increase the risk for epithelial ovarian cancer but is unlikely to be the etiology for the majority of epithelial ovarian cancers." The sponsor of this study was the National Cancer Institute.

The second meta-analysis was conducted by Gross and Berg [37] and was published in 1995 and included data from 9 separate papers [15-23]. This meta-analysis yielded a summary odds ratio (based upon the crude measures) of 1.27 (1.09, 1.48)—again statistically significant. No significant heterogeneity was observed. Gross and Berg concluded that the data regarding the association with talc and ovarian cancer was "equivocal." This study is acknowledged as supported in part by Johnson and Johnson.

The third meta-analysis was performed as part of my 1999 paper [29] on talc and ovarian cancer. It included all of the studies in the Gross and Berg paper [37] plus four new studies [24-27] as well as the OR based upon a new series of 563 cases with ovarian cancer and 523 controls from Massachusetts and New Hampshire. The summary odds estimate was 1.39 (1.24, 1.49), again statistically significant. The conclusion of this study was that we found a significant association between use of talc in genital hygiene and risk of ovarian cancer that, "when viewed in perspective of published data on this association, warrants more formal public health warnings." This paper was supported by a grant from the National Cancer Institute.

The fourth meta-analysis was performed by Huncharek, Geschwind, and Kupelnick [38] in 2003 and included all of the studies examined in my meta-analysis except for a study by Hartge [16] and one by Shushan [25]. Data from 5 new studies [28-32] were also included giving a total of 16. The summary odds ratio from this meta-analysis was 1.33 (1.16 -1.45)—once again significant. However, Huncharek et al. concluded that the available observational data "do not support the existence of a causal relationship" between talc use and an increased risk of epithelial ovarian cancer. In the Acknowledgements, it is stated that partial support for the work was provided by the Marshfield Medical Research Foundation. A subsequent paper in 2007 related to talc and authored by Huncharek and Kupelnick cites support from Johnson and Johnson and Luzenac America [39].

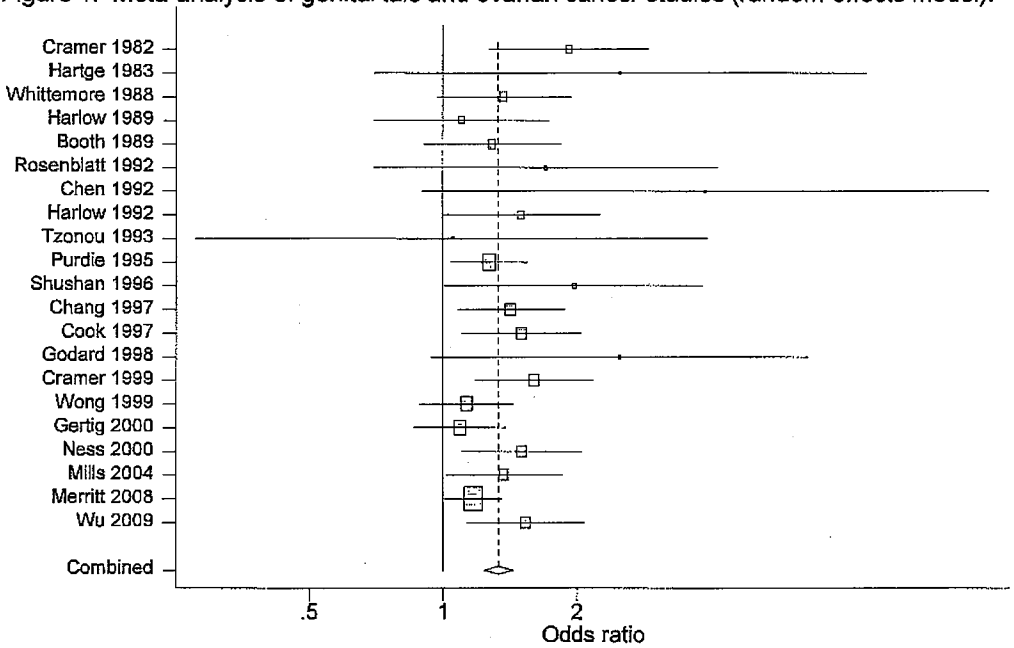
The fifth meta-analysis was performed in connection with the review conducted by the International Agency for Research on Cancer regarding talc use and ovarian cancer [40] and included prior epidemiologic studies and additional data from a study of benign ovarian tumors [41]. The estimated summary OR differed little from that of the Huncharek meta-analysis, but the authors concluded the evidence was sufficient to indicate cosmetic talc is a "possible carcinogen."

A few minor issues can be raised related to the odds ratios chosen to represent genital use in several of these meta-analyses. The OR for the association in the Rosenblatt study [21] was taken as 0.84 (0.27, 2.63) based upon any "genital fiber use" which included possible (but not certain exposure) from prior pelvic surgery, use of a diaphragm or condoms, as well as powdering the genital area after bathing or showering or use on sanitary napkins--the latter two definitions being used in most studies. The crude odds ratio for more certain genital exposure from powdering after bathing or use on sanitary napkins is 1.7 (0.7, 3.9) (see Table 3 in Rosenblatt paper). The odds ratio for the Hartge study [16] is listed as 0.7 (0.4, 1.1) based upon "any talc" which included use of talc in non-genital areas. The odds ratio for use in the genital area was 2.5 (0.7, 10.0) (see Table in letter). Finally, in the Wong et al. study [30], the odds ratio of 1.0 (0.8, 1.3) was selected to represent genital talc use whereas this was only one of several categories related to genital exposure (see Table 2). A more appropriate odds ratio for ever vs. never genital exposure in the study by Wong et al would be 1.13 (0.89, 1.43).

These changes would have little impact on the summary OR estimates or levels of significance in the meta-analyses.

Since Huncharek's meta-analysis in 2003 [38], there have been 4 additional epidemiologic studies (with original data in 3) related to talc and ovarian cancer. All found a positive association [30-36] Thus, if we construct a new meta-analysis based on ever vs. never genital exposure using the appropriate odds ratios for Rosenblatt, Hartge, and Wong, the summary OR (and 95% limits) is 1.33 (1.24, 1.43) using a random effects model or 1.32 (1.23, 1.41) from a fixed effects model. The "z value" associated with this is 7.6 in the random effects model and 7.9 from the fixed effect model. The associated p value reflecting the likelihood that this odds ratio is significantly different from 1 is about 10^{-14}. No significant heterogeneity is noted between the study estimates (p=0.36), although it has been pointed out that ORs from hospital-based studies might be lower than population-based studies [38, 40].

Figure 1. Meta-analysis of genital talc and ovarian cancer studies (random effects model).



The talc and ovarian cancer association—cause and effect?

Clearly, only if there is reasonable likelihood that the association between talc use and ovarian cancer found in epidemiologic studies is causal, can a connection between talc use and ovarian cancer in Ms. Berg's case be argued. The well-known British statistician Sir Austin Bradford Hill is credited with establishing the criteria that epidemiologists often use in judging whether an association is likely to be causal. Hill originally listed 9 criteria which have been restated over the years, but, in one form or another, are considered when regulatory or legal issues arise in connection with an epidemiologic association. In a paper entitled "Causation and Disease: Biomedical Science in Toxic Tort Litigation," Muscat and Huncharek list 8 criteria [42]. In connection with a meeting on the carcinogenicity of talc held in 2000 by the National Toxicology Program, epidemiologists Rothman, Pastides, and Samat (Attachment 2) mention 8 issues and discussed 5 in detail while another epidemiologist, Samuel Shapiro cited 11

criteria that should be addressed. The latter two critiques focused heavily on a consideration of errors of study design and analysis, which were not part of Hill's original criteria. I consider the following criteria most important: statistical significance, reverse causality, consistency, effect of removing the causal agent, bias and confounding, strength of the association, dose-response, and biologic credibility.

1. Statistical significance of the association. Could chance have accounted for the observations? The lower confidence bound of the summary odds ratios from each of the meta-analyses conducted exceed the value of 1 (the indicator of no association) and thus indicate a statistically significant association. In the critique by Rothman et al., they state "We omit discussion of the role of chance in explaining any of the findings, because the combined weight of the 17 studies in (their) Figure 1 indicates that chance alone is an unlikely explanation for the overall weighted average of relative risks from the studies of 1.31." Chance is an unlikely explanation indeed—about 1 in a trillion based upon our most recent meta-analysis.

2. That exposure precedes the disease is an obvious requirement. However, in a case-control study where subjects are interviewed about exposures after their disease is diagnosed, it is conceivable that cases may cite exposures that began because of symptoms or treatment of their illness thus producing "reverse causality." However, epidemiologists who conduct case-control studies are well aware of this pitfall, do not count exposures begun after the illness was diagnosed, and generally censor exposures for some time period prior to disease diagnosis (1 year in studies I have done). I believe it very unlikely that talc use begun 20 years prior to the diagnosis of ovarian cancer occurred because of symptoms of latent disease. Rothman et al. comment "we do not think it (reverse causation) is a realistic explanation for the observed effect." This is my opinion as well.

3. Consistency. Consistency is a characteristic of associations repeatedly found by different investigators in different populations or studies of different designs. The talc association has been found in geographically and ethnically diverse populations from United States, Canada, England, China, and Australia, in hospital-based and population-based case-controls studies, and in a cohort study. The meta-analyses have yielded similar and consistent evidence for an association without significant heterogeneity over all studies. In my opinion, the criterion for consistency is met.

4. Removal of the agent results in a reduction of disease frequency. In diseases caused by infection, showing that treatment of the infection or protection by vaccination cured or prevented the disease would satisfy this criterion. In chronic disease epidemiology, this criterion might be addressed by showing a correlation between calendar year and disease occurrence for an exposure relatively limited in time. Apparently there has been some decline in domestic production of cosmetic talc since 1980 [43]. However, it would be a difficult epidemiologic task to relate this to changes in ovarian cancer rates because: it is not known what the latency for talc use to lead to ovarian cancer might be; other temporal changes have occurred such as increasing use of birth control pills and declining fertility, and even changes in national statistics (the National Cancer Institute stopped counting borderline tumors as ovarian cancers around 2005.) It has also been suggested that the mid-1970's represented a watershed time period after which possible asbestos contamination of talc was eliminated by self-monitoring within the cosmetics industry. Some epidemiologic studies have attempted to distinguish the effect of talc use before or after this period, but no consistent change in odds ratios based on a cutoff

around this time has been demonstrated [20, 27, 33, 36]. In my opinion, this criterion cannot be invoked either to confirm or refute a causal association.

5. The association is unlikely to be due to systematic errors in study design and analysis. The particular errors I will discuss are misclassification, recall bias, selection bias, and confounding. Misclassification means that subjects have been misclassified by disease status or, more likely, by exposure status. For any epidemiologic study, it is necessary to identify "exposed" and "non-exposed" so the questions used to define those states are critical. In the case of smoking, a commonly used question to assess exposure is: "Have you smoked more than 100 cigarettes during your lifetime?" However, there is no agreement on the standard language that should be used to assess genital talc exposure. Thus the question "did you ever use cosmetic powder containing talc?" may yield a different answer than "did you regularly use cosmetic powders containing talc in your genital area?" that, in turn, may differ from the response to an even more specific question "did you regularly apply cosmetic or baby powders containing talc to your genital or rectal area after bathing or showering or use powder to dust underwear or sanitary napkins?" Because of this lack of standardization, there is the potential for misclassification from study to study. Random misclassification would move the association towards the null value of 1 and could not account for a positive association observed in studies. If anything, random (or non-differential) misclassification would have led to an underestimate of the effect. A bias of greater concern in case-control studies is differential misclassification. If cases are more likely to admit to or remember exposures more readily than controls, then recall bias might occur and the odds ratio could be falsely elevated. I think it is unlikely a woman would be embarrassed to reveal she had used talc; and, while short term use might be more readily recalled by cases than controls, I believe long term talc use (more than 10 years) would not be forgotten by either cases or controls. Finally, if there were recall bias, it might be anticipated that ORs for studies done more recently would drift higher with cases having had more opportunity to have heard about the association. The ORs in Figure 1 (organized by calendar year of the study) do not reveal any drift higher in more recent studies.

In a case-control study, it is usually not possible to study all cases (and certainly not all controls) in either a population or hospital-based study. Thus, there is the possibility that cases or controls could be selected whose exposure histories do not represent those of the broader populations we wish the sampled subjects to represent. In their review, Rothman et al thought selection bias was a "less important" issue and omitted it from their discussion. Selection bias (as well as reverse causality and recall bias) are less likely to occur in cohort studies. Notably, the cohort study of talc and ovarian cancer from the Nurses' Health Study observed a significant association with invasive serous cancer [32].

Confounding is an issue that can affect either case-control or cohort studies and occurs when some factor associated both with the illness and the exposure has not been considered and corrected for in the design of the study or analysis of the data. Most of the talc studies have adjusted for age and known risk factors for ovarian cancer, such as parity or oral contraceptive use, even though reproductive factors are not known to be associated with talc use. A 1998 paper by Rosenblatt identified body mass index (BMI), smoking, and alcohol use as potential correlates of talc use in the general population [44]. Weight or BMI was adjusted for in several of the studies with the ORs remaining significant [20, 29, 34]. Although I don't believe any studies have adjusted for smoking and alcohol use, my opinion is there is no reason to link these exposures to risk for

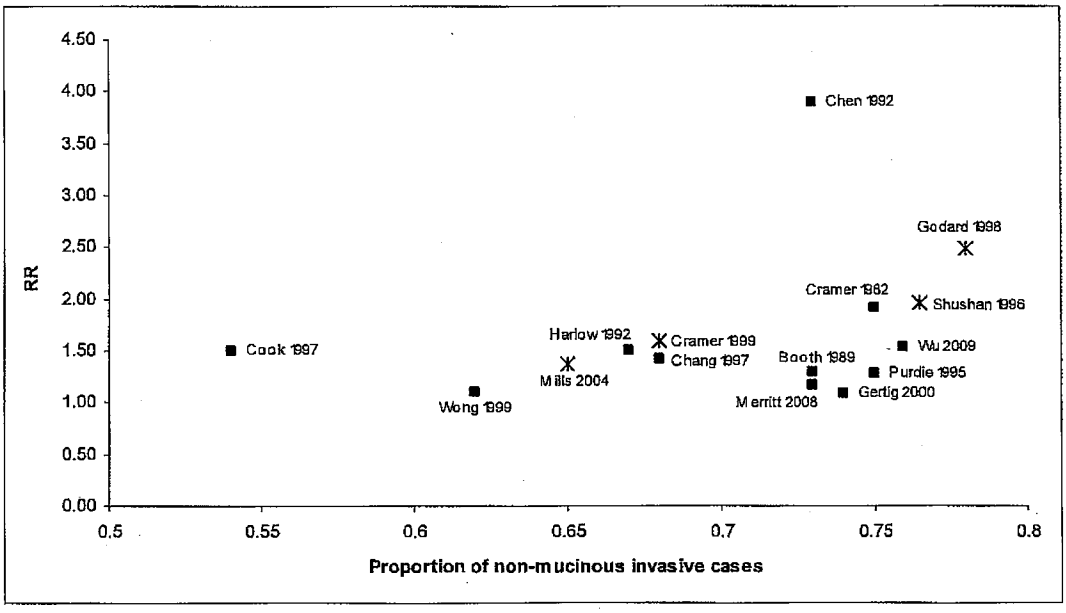
ovarian cancer except possibly for mucinous ovarian cancers [45], for which the association with talc use is less apparent (see point 6). Also, if characteristics of powder users rather than powder use itself increases risk for ovarian cancer, then it would be anticipated that women who used cornstarch based powders would also be at increased risk, which does not appear to be the case from a study which looked at cornstarch powder use in the talc studies that had examined this. [46]

My conclusion regarding bias and confounding is that these could not have produced a totally spurious effect over all of the studies.

6. The association is strong. A summary odds ratio of 1.33 (1.23, 1.44) indicates that we expect the risk for all types of epithelial ovarian cancer to be raised by an average of 33% (or somewhere between 23 to 44%) by ever use of talc in genital hygiene. A OR of 2 is sometimes set as a benchmark as the minimum for associations likely to be causal [42]. I would challenge the argument that risks less than 2 can't be causal and also point out that an overall summary risk less than 2 does not rule out a stronger association for certain types of ovarian cancer, certain categories of exposure, or for women with certain characteristics. The question of whether an association <2 can be causal is, I believe, addressed by recent genome wide association studies (GWAS) which test hundreds of thousand genetic variants called single nucleotide polymorphic variants (SNPs) in cases and controls. GWAS studies have revealed gene polymorphic variants that individuals are born with that may increase the risk for various cancers including ovarian cancer. As opposed to relatively rare mutations of the BRCA1 and BRCA2 genes which may increase risk for ovarian cancer some 30 to 40 fold (3000 to 4000%), cancer-associated SNPs occur with higher frequency but may change the risk for cancer only 15% to 20%. Thus, SNPs rs8170 and rs2363956 on chromosome 19 have been associated with ORs of 1.16 and 1.18 for serous ovarian cancer, respectively, and are almost certain to be real based on three phases of evaluation in over 5,900 cases and 13,000 controls and p values of 10^{-9} and 10^{-11}, respectively [47]. Compared to these GWAS findings, I point out that the summary OR for the talc/ovarian cancer association and its p value are "stronger" and more significant.

Also important in the interpretation of the 1.33 overall association between talc and ovarian cancer is whether the strength of the association may differ for certain types of ovarian tumors or in subjects with certain characteristics or different degrees of exposure. Studies which looked at the association by histologic type of ovarian cancer have found the talc association is weaker in women with mucinous ovarian tumors (especially "borderline malignant" types) and stronger in non-mucinous invasive ovarian cancer. I reviewed the studies in my meta-analysis to find the percent of non-mucinous invasive tumors in each. When the proportion of histologic types was given but was a mixture of borderline and invasive cases, I applied the appropriate proportions from our own case-control data where 78% of all serous types were invasive and 95% of all non-serous and non-mucinous cases were invasive and estimated the study specific proportion of non-mucinous invasive cases. Overall there was a non-significant (p=0.31) positive correlation between the percent of non-mucinous invasive tumors and the OR estimate such that studies with a greater estimated percentage of non-mucinous invasive tumors had higher ORs (Figure 2). The studies marked with asterisks in the figure below are the 4 studies [25, 28, 29, 33] in which the percent of non-mucinous invasive tumors was explicitly stated in the text. The correlation in this small set was r=0.94, p=0.06.

Figure 2. Genital talc risk ratios reported in studies by proportion of non-mucinous invasive cases.



Not only characteristics of the tumors but also characteristics of the subjects should be examined for their effects on OR estimates. Thus one recent study has suggested that genetic determinants such as those influencing the body's reaction to inflammation may also affect the talc association [34]. Age is an even more basic factor that may influence overall estimates. While most studies have adjusted for age, it may be necessary to actually show the association in various age categories to determine if the association is greater in one age group compared to another. Finally the association may be stronger for women with a higher level of exposure. I will return to both of these issues, interaction with age and strength of the association with greater exposure, in point 7.

In concluding my discussion of strength of the association as a criterion, I restate the fact that GWAS studies reveal that SNPs that predispose to disease risk are usually associated with risk measures less than 2 but are likely to be causal. Thus, in my opinion, there is no scientific basis for setting a minimum bar for defining a causal association. I have also pointed out that an overall summary risk less than 2 does not rule out a stronger association for certain types of ovarian cancer, certain categories of exposure, or for women with certain other characteristics. It is my opinion an overall association of 1.3 between talc use an ovarian cancer risk is "strong" enough to be causal, especially if the final two points to be discussed—dose-response and biologic credibility—are satisfied.

7. There is a dose-response. A dose-response (or biologic gradient) refers to a consistent increase (or decrease in the case of a protective exposure) in risk corresponding to levels of the exposure. I pointed out that whether there is an association is addressed by a simple "yes" or "no" answer to a question about exposure (see discussion of misclassification under point 5). Women who answer "yes" they used talc should then be asked additional questions about frequency and duration of use. To categorize dose-response as precisely as possible, one should combine both frequency and duration together to yield application-years (or total lifetime applications) similar to

what is done for smoking when a "pack-years" variable is calculated (i.e., number of packs per day smoked x number of years smoked).

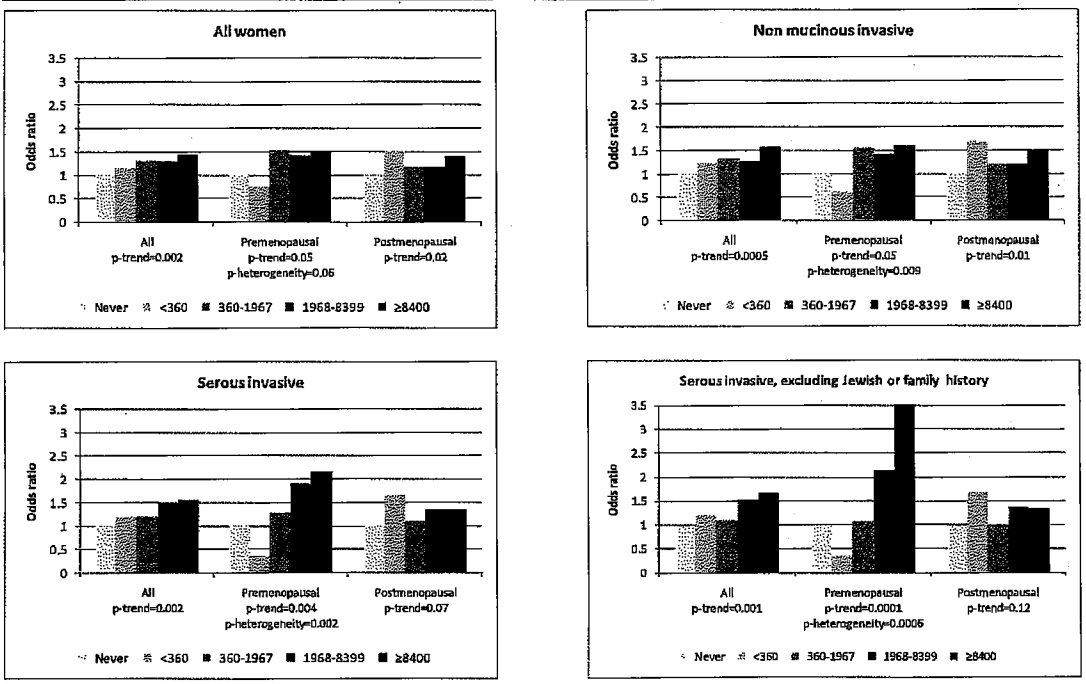
Apparent lack of dose-response as a key factor undermining a causal interpretation for the ovarian cancer and talc association has been highlighted in industry-sponsored research by Rothman et al. and Huncharek et al. [38]. In both of their reports, data was included on years of talc use and number of talc applications per month. However, no data was provided on a measure which combined both frequency and duration of use (as would be needed for the equivalent of pack-years of smoking). A woman who used talc daily for one year would have 365 applications compared to 2400 for a women using talc 10 times a month for 20 years. The level of exposure for these two cases might well be reversed in separate tables related to duration and frequency of use. In two of our papers [20, 29] we showed that adjusting the applications variable for whether the genital tract was "open" (i.e. not counting use after a tubal ligation or hysterectomy and looking at use during times when ovulation was occurring) yielded a statistically significant dose-response

In more recent papers [33-36], data is available for dose-response in all of them. Mills found a significant dose-response by frequency of use, duration of use, and estimated applications [33]. Wu, looking at all types of body use, found a significant dose-response with estimated applications [36]. Merritt reported a significant trend in risk for invasive serous ovarian cancer with years of talc use [35]. Gates et al. pooled data from the Nurses' Health Study and the two prior phases of our case-control study and found a significant trend with frequency of talc use per month (the only "dose" data available in the Nurses' Health Study data) [34].

A consideration that affects dose-response is that it is difficult to separate entirely duration of use (or total applications) from age. A 25 year-old woman cannot have had 30 years of talc use; and 30 years of use is more likely for a 60 year-old than for a 40 year-old. Thus, if there were differences in the strength of the association between younger and older women, this could obscure a dose-response even if the trend statistic were adjusted for age. To reveal this, it is necessary to show the association in the younger and older age groups. It is known that breast cancer risk factors, like BMI, may differ by menopausal status. Menopausal status may also affect the association for some risk factors for ovarian cancer, including BMI and coffee consumption [45, 48]. Although I adjusted for menopausal status in our first study, I never showed the association separately for pre- and postmenopausal women nor has this been done in any of the other 21 studies to date. In Attachment 3, using my own case-control data, I looked at the overall association and dose-response in all women and then for pre- and postmenopausal women separately for all types of ovarian cancer combined. These analyses were then repeated for non-mucinous invasive types of ovarian cancer and serous invasive ovarian cancer. The overall association is stronger for non-mucinous invasive cases and invasive serous cancer compared to all types of ovarian cancer that includes borderline malignancies. Inportantly, for invasive serous cancers, there is a sharpening of the dose-response curve for premenopausal compared to postmenopausal women. Because a genetic factor should be considered in the cause of premenopausal ovarian cancer, I show as the final table in Attachment 3 an analysis for serous invasive cancer excluding those with a family history of ovarian cancer or early onset breast cancer or women with a Jewish ethnic background (who have a higher background rate of BRCA1/2 mutation). After these exclusions, the OR (and 95% limits) are 2.12 (1.16, 3.89) for premenopausal women with about 2000 to 8400 applications

and 3.53 (1.63, 7.65) for women with greater than 8400 applications compared to women with no genital talc exposure. This sharpening of the dose-response is illustrated in Figure 3 below which was presented as part of a poster at the 2011 Annual Meeting of the American Association of Cancer Research (Attachment 4). I believe this demonstrates that the dose-response has been underestimated in all prior studies (including my own) by the failure to take into consideration histologic subtype of ovarian cancer, menopausal status, and family history in a systematic fashion.

Figure 3. Dose-response associations for talc applications by histologic type of ovarian cancer, menopausal status, and family history.



Concluding my remarks related to dose response, I point out that a measure combining both frequency and duration of use needs to be considered. Furthermore, heterogeneity in the case mix of histologic types from study to study might weaken dose-response. Larger and more recent studies do reveal a significant dose-response. Finally, my new analysis reveals that the dose-response was likely further underestimated by the failure to take into consideration menopausal status and family history. When this is done, there is a strong dose-response in premenopausal women for invasive serous ovarian cancer. In my opinion, the criterion for a dose-response is satisfied.

8. Biologic Credibility. Biologic credibility requires that we ask whether the association makes biologic sense in terms of what is known about the biology of the cancer or the exposure and whether animal or cell line experiments support an association. In my original paper [15], I cited four elements as the foundation for the biologic argument linking talc and ovarian cancer: chemical relationship between talc and asbestos, asbestos as a cause of pleural and peritoneal mesotheliomas, the possible relationship between ovarian cancer and mesothelioma, and the ability of talc to enter the pelvic cavity. In my paper. I acknowledged that the carcinogenicity of asbestos depends upon

its fiber-like structure which is different from the plate-like structure of talc but stated that it wasn't clear whether the link between talc and ovarian cancer related to asbestos contamination of talc powders or to the uniqueness of the ovary that might make it susceptible to either asbestos or talc. Another element of the argument, the similarity between ovarian cancer and mesothelioma, has been emphasized by the Grahams [1] and the Johns Hopkins gynecologic pathologist and surgeon, J. Donald Woodruff [49]. Regarding the evidence that talc used in the genital area can reach the ovary, I believe that the most convincing studies were done in humans and demonstrated that carbon (bone) black ink placed into the vagina prior to hysterectomy could be demonstrated microscopically in washings from the tube or even seen with the naked eye in some cases [50, 51]. Radiolabeled albumen microspheres placed in the vagina also reached the Fallopian tubes in women [52]. I believe talc found "deeply embedded" in ovarian tissue [6] cannot be attributed to artifacts of processing and speaks for itself regarding the issue of translocation. Although some studies of non-human primates have attempted to address the issue of translocation [53], [54], these studies cannot duplicate the decades long exposure that women may have. In my opinion, these studies do not disprove talc can reach the upper genital tract and cause changes predisposing to ovarian cancer. At least one cell culture experiment does show that talc is capable of causing proliferative changes in ovarian cell cultures indicative of malignancy—an effect that could be antagonized by an anti-inflammatory agent, suggesting a role for inflammation and reactive oxygen species in the talc and ovarian cancer association [55].

While I believe that the foundations for our original argument for biologic credibility for the talc and ovarian cancer association remain intact, an emerging model for ovarian cancer involving acute and chronic inflammation and immunity can also explain why talc might cause ovarian cancer. After observing that fewer of our ovarian cancer cases had a breast infection (mastitis) compared to controls [56] and finding a report describing antibodies against a surface mucin protein called MUC1 following breast mastitis [57], we hypothesized that MUC1 immunity could explain ovarian cancer risk factors. We tested this theory by measuring anti-MUC1 antibodies in controls from the second phase of our case-control study, determining what events were associated with anti-MUC1 antibodies, and then looking at whether those events were risk factors for ovarian cancer. Factors that elevated anti-MUC1 antibody levels included mastitis, a tubal ligation, and IUD use and these were factors that decreased ovarian cancer risk in our study. Factors that raised ovarian cancer risk were those that lowered anti-MUCI antibodies and included talc use and an increasing number of ovulatory cycles not interrupted by oral contraceptives, pregnancies or breastfeeding [56, 58].

We then performed a prospective study in which we measured anti-MUC1 antibodies in specimens taken at least 3 years prior to diagnosis in ovarian cancer cases and matched controls from the Nurses' Health Study. This study confirmed findings that tubal ligation raised antibody levels and a greater number of ovulatory cycles lowered antibody levels [59]. Talc use also lowered antibodies but the finding was of borderline significance. In this study, the presence of anti-MUC1 antibody levels at least three years before diagnosis predicted a lower risk for ovarian cancer in women less than age 64. A protective effect of antibodies was not apparent in women older than 64. I attributed this age-dichotomy to the combination of a general decline in immunity in controls that occurs with aging (immunosenescence) and an apparent increase in antibody levels in older cases, which I believe reflects the fact that women with the lowest MUC1 immunity having their ovarian cancer diagnosed at a younger age. The

possible link between immunity, MUC1, and talc use could now explain the difference in dose-response between pre- and postmenopausal women. Ovarian cancer may occur at a younger age in long-term talc users whose immunity has been most suppressed, explaining why the dose-response is much stronger for pre- than postmenopausal women. Those "susceptible" have already been depleted leaving fewer long term talc users in the postmenopausal group. A similar epidemiologic phenomenon was described as far back as 1938 to explain why the associations between smoking, total mortality, and coronary artery disease incidence are stronger in younger compared to older men [60, 61].

Recalling the curious protective effect of mumps parotitis described by Newhouse [13], I performed a study on blood specimens from people going through a mumps infection and found that mumps also generates anti-MUC1 antibodies [62]. Thus, my current theory is that ovarian cancer occurs due to a relative absence in younger life of events which led to beneficial MUC1 immunity, such as mumps, mastitis, or tubal ligation, and an excess of chronic events, like ovulatory cycles, endometriosis, and talc use which down regulated MUC1 immunity and led to immune tolerance of an emerging cancer. Our case report showing that talc can be found in the lymph nodes of an ovarian cancer patient who used talc suggests this could be an additional mechanism by which talc might effect local immune processing [63]. Case reports describe talc in lymph node and tissues of IV drug abusers who inject drugs cut with talc and link this with decreased systemic immunity [64].

To conclude, I believe the following elements support biologic credibility of the talc and ovarian cancer association:

1) Talc is a potent inflammatory agent that may lead to dysregulation of immunity related to mucins, especially MUC1, by chronic irritation of vaginal epithelium which, like surface cells of the endometrium or Fallopian tubes, expresses MUC1 in response to environmental stressors.
2) As opposed to short term expression of an inflammatory form of MUC1 which can lead to protective antibodies, chronic expression of the inflammatory form of MUC1 leads to down regulation of MUC1 immunity and tolerance of an emerging MUC1-expressing cancer (which ovarian cancer is).
3) By this mechanism, talc use fits with other events, such as repeated ovulatory cycles and endometriosis that increase ovarian cancer risk through a chronic inflammatory pathway [65].
4) Used externally, talc reaches the lower genital tract, may be phagocytized by inflammatory cells, and trapped in pelvic lymph nodes where it may further dysregulate local immune processing.
5) Talc likely reaches higher into the upper genital tract further disrupting mucin immunity in the tubal epithelium and possibly transforming tubal or ovarian epithelium.
6) A stronger dose-response with talc in pre-menopausal women is compatible with the observation that impaired MUC1 immunity may affect susceptibility to ovarian cancer such that it occurs at a younger age. In turn, this may blunt the dose-response in older postmenopausal women because those most susceptible to the effects have left the at-risk pool.
7) Talc is carcinogenic, if only, by its ability to induce inflammation, down regulate immunity, and enhance ovarian tumor development.

Agency Opinions

The National Toxicology Program (NTP) nominates agents for consideration of carcinogenicity in their Report on Carcinogens (RoC) on the basis of recommendation from internal review panels. An external review panel is then formed in which testimony for or against the nomination is presented including that by industries that may be affected. Internal reviews nominated talc be considered for carcinogenicity in both its 2000 and 2004 reports. Talc was considered in the 10th ROC in 2000, and the external panel voted 3 for and 7 against declaring talc a carcinogen. NTP decided to reconsider the issue again for its 12th report in 2004 since apparently part of the issue for the 10th report was which form of talc should have been considered. In 2004, the issue mostly addressed cosmetic talc and ovarian cancer. The vote was 2 for and 8 against declaring talc carcinogenic in this setting. Sometime in late 2004 or early 2005, I was asked by a consulting group affiliated with NTP to provide an opinion about talc and ovarian cancer for a new RoC meeting being planned to resolve the talc issue. I received some materials related to the 2004 meeting, including the Rothman and Shapiro reports from 2000 and letters from the Cosmetic, Toiletry, and Fragrance Association and CRE (Center for Regulatory Effectiveness) to Dr. Jameson critical of NTP for its handling of talc in their nomination process. Although I expressed my willingness to provide an opinion, I learned after several months had passed that NTP had withdrawn their nomination for talc as a carcinogen.

The International Agency for Research on Cancer (IARC) has also considered the carcinogenicity of talc—most recently in 2005. Industry generally has less involvement in the IARC meetings. In 2005, IARC voted in favor of declaring cosmetic talc a group 2B agent, "possibly carcinogen to human beings." [66]. Neither NTP nor IARC had the opportunity to consider my recent observations about talc, MUC1 immunity, and lymph nodes and obviously were not aware of the differences in dose-response between pre- and postmenopausal women.

The Role of Talc in the case of Ms. Deane Berg

In 12/2006 at the age of 49, when she was still premenopausal, Ms. Deane Berg was diagnosed with high-grade invasive serous cancer of the ovaries (Attachment 5). This is the most common type of invasive ovarian cancer occurring in about 42% of women diagnosed with ovarian cancer. Less common, Ms. Berg falls into the approximate 25% of women who develop this type of tumor premenopausally. A familial or genetic tendency is often considered when a woman develops breast or ovarian cancer under age 50, such as a mutation in one of the two predisposing breast and ovarian cancer (BRCA) genes. Indeed, about 40% of Jewish women who develop ovarian cancer at a relatively young age will have one of the three common mutations found in about 2% of Jewish women. However, Ms. Berg is not Jewish, had no family history of breast or ovarian cancer or personal history of breast cancer, and tested negative for the full panel of BRCA1 and BRCA2 mutations in July 2007 (Attachment 6).

In January 2011, we interviewed Ms. Berg by phone and administered the same questionnaire we used in the most recent phase of our case-control study. Ms. Berg was specifically asked to include only those exposures which occurred one year prior to the date of the diagnosis of her cancer. A copy of the completed questionnaire is included as Attachment 7. In response to our question about the use of talc, Ms. Berg

indicated that she had used Johnson and Johnson baby powder or Shower to Shower (another Johnson and Johnson product) on a daily basis between the ages of 16 to 48 (we excluded use in the year prior to diagnosis). This would mean Ms. Berg had applied talc to her genital area more than 11,000 times. I do not count here possible exposure from a diaphragm which she said she had used for about 4 years, nor possible exposure from condoms used for a total of 12 months. Clearly the amount of potential talc exposure from these sources is minimal compared to her daily use in the genital area.

In reviewing Ms. Berg's questionnaire data, the other major factors I note related to her risk for ovarian cancer included her lack of birth control pill use and lack of breastfeeding—both of which would lead to a higher number of ovulations. Ms. Berg related that her mother died of a stroke at 38 possibly due to oral contraceptives which would have been viewed as contraindication for her own use of oral contraceptives. She did not breastfeed because she required anti-seizure medications following head injury as a teenager. In terms of protective factors, Ms. Berg did have a tubal ligation about 3 years prior to diagnosis. Her history of mumps could also have been a favorable risk factor. Looking at Table 4 below to define her risk for ovarian cancer constructed from our own case-control data, Ms. Berg falls into the category of more than 8400 applications for premenopausal women with invasive serous ovarian cancer

Table 4. Association between genital talc use and ovarian cancer among non-Jewish serous invasive cases and controls without a family history of ovarian or early onset breast cancer, stratified by menopausal status.

Talc use	All subjects N_{cases}=686 $N_{controls}$=1839		Premenopausal N_{cases}=173 $N_{controls}$=769		Postmenopausal N_{cases}=513 $N_{controls}$=1070		Interaction p
	OR (95% CI)[1]	P	OR (95% CI)[1]	p	OR (95% CI)[1]	p	
Never	1.00		1.00		1.00		0.66
Ever	1.39 (1.14, 1.69)	0.001	1.36 (0.91, 2.03)	0.13	1.35 (1.07, 1.70)	0.01	
Applications							
Never	1.00		1.00		1.00		0.0006
<360	1.20 (0.82, 1.75)	0.36	0.34 (0.12, 0.91)	0.03	1.68 (1.08, 2.62)	0.02	
360-1967	1.09 (0.76, 1.56)	0.64	1.08 (0.52, 2.22)	0.84	1.02 (0.67, 1.56)	0.92	
1968-8399	1.53 (1.10, 2.14)	0.01	2.12 (1.16, 3.89)	0.01	1.35 (0.90, 2.02)	0.15	
≥8400	1.65 (1.19, 2.30)	0.003	3.53 (1.63, 7.65)	0.001	1.34 (0.93, 1.94)	0.11	
p-trend[2]		0.001		0.0001		0.12	0.0008
p-trend[3]		0.18		0.001		0.87	

[1]Adjusted for study phase and center, reference age, parity, OC use, tubal ligation, BMI, smoking history, and alcohol use.
[2]Trend p-value includes never users.
[3]Trend p-value excludes never users.

who did not have a family history of breast or ovarian cancer. The risk for women with these characteristics is 3.53. The trend is significant whether non-use is considered the referent or whether the dose-response is restricted to users.

In tort litigation, an "etiologic fraction (EF)" is calculated from relative risks (RR) or odd ratios according to the formula: EF = (RR -1)/RR [42]. An EF greater than 50% is considered to satisfy the "preponderance rule" to show the exposure was more likely than not to have caused the disease. In the case of Ms. Berg, the etiologic fraction is 72%; i.e. [(3.53-1)/3.53].

Conclusion

In this report, I have reviewed the epidemiologic evidence supporting an association between cosmetic talc use in the genital area and risk for ovarian cancer. I have sought to show how the talc association with ovarian cancer meets major criteria for a causal association including: statistical significance, cause precedes effect, consistency, absence of bias and confounding, strength of the association, dose-response, and biologic credibility. The overall estimate of the association from meta-analyses is stronger and more significant than genetic associations from Genome Wide Association Studies, accepted by the scientific community as real. Importantly, I have shown that the strength of the association and the dose-response have been under-estimated by the failure to take histologic type of ovarian cancer, menopausal status, and family history into consideration. Premenopausal women with invasive serous cancer and no family history have a strong and highly significant dose-response with number of talc applications. In terms of biologic credibility, at least two models can explain why talc use might cause ovarian cancer including its properties as an inflammatory agent with effects on the immune system. Based upon my review of this evidence, it is my opinion to a reasonable degree of epidemiologic certainty that there is a causal association between the use of talc and ovarian cancer. In Ms. Berg's specific case, it is my opinion to a reasonable degree of medical and epidemiologic certainty that chronic talc use was the major cause of her invasive serous ovarian cancer that occurred at age 49.

It has been about 40 years since talc producers, the cosmetics industry, in general, and Johnson and Johnson, in particular, have been aware of a possible connection between cosmetic talc use and ovarian cancer. Had a warning label been placed on talc products in 1982 discouraging use in the genital area, Ms. Berg might have stopped her talc use and avoided more than 20 years of exposure. Sadly, that did not happen—the consequence of which, in my opinion, is the invasive serous ovarian cancer that she developed.

Daniel W Cramer

8/24/11

Daniel W. Cramer, MD, ScD **Date**

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Attachments

1. Details of Epidemiologic studies

2. Critique of the talc association by Rothman, Pastides, and Samet

3. Investigation of the effect of histologic type, menopausal status, and family history of ovarian or breast cancer on the talc association.

4. Poster from AACR

5. Path Report from primary surgery original in Ms. Berg

6. Report of BRCA1/2 testing in Ms. Berg

7. Ovarian Cancer Questionnaire with Ms. Berg's responses.

Attachment 4

Talc use and ovarian cancer: Influence of histologic type and menopausal status on strength and dose-response of the association

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Introduction

More than 20 epidemiologic studies support an association between talc powder use in the genital area and ovarian cancer; yet causality of the association has been challenged partly because of an apparent lack of a dose-response (1). To determine whether this aspect of the association has been affected by the failure to consider, in a uniform fashion, histologic type of ovarian cancer, menopausal status, or family history, we examined data from our New England Case-Control study that includes data on talc use from more than 2000 ovarian cancer cases and 2000 controls.

Methods

Data come from three phases of a case-control study of ovarian cancer in New England. We identified ovarian cancer cases diagnosed in Eastern Massachusetts and all of New Hampshire from May 1992-March 1997, August 1998-April 2003, and October 2003-November 2008 (2,3). We enrolled 2,203 cases of whom 2,076 had been diagnosed with epithelial ovarian cancers. Controls for the first phase of the study were identified by random digit dialing (n=421) supplemented with residents' lists for older controls. All controls for the second and third phases were identified through town residents lists in Massachusetts and Driver License Registries in New Hampshire. Of 4,625 potential controls identified through town books in both phases, 1,495 were ineligible, 1,460 declined participation, and 1,680 were enrolled. In total, 2,101 controls were enrolled. After written informed consent, demographic details, medical and reproductive history, and habits were assessed by personal interview. Questions were framed with respect to a reference date defined as 1 year before the diagnosis date for cases or date of interview for controls. This study is approved by the Brigham and Women's Hospital and Dartmouth Medical Center Institutional Review Boards (IRB).

We used logistic regression to study the association between ovarian cancer and regular use of genital talc as well as total applications (estimated from frequency and duration of use), adjusted for study phase, study center, age, parity, oral contraceptive use, tubal ligation, BMI, smoking, alcohol use, Jewish ethnicity, and family history of breast or ovarian cancer. Separate analyses were done for all cases, non-mucinous invasive cases, serous invasive cases, and serous invasive cases unlikely to have been familial.

Results

Table 1A. Talc association in all histologic types including borderline tumors by menopausal status.

Talc use	All subjects				Premenopausal				Postmenopausal				Interaction
	Controls N=2099	Cases N=2074	OR (95% CI)[1]	p	Controls N=887	Cases N=850	OR (95% CI)[1]	p	Controls N=1212	Cases N=1223	OR (95% CI)[1]	p	p
Never	73.4%	68.1%	1.00		78.4%	73.4%	1.00		69.8%	64.4%	1.00		0.99
Ever	26.6%	31.9%	1.30 (1.13, 1.49)	0.0003	21.6%	26.6%	1.23 (0.97, 1.56)	0.08	30.2%	35.6%	1.31 (1.10, 1.56)	0.003	

Table 1B. Talc association in non-mucinous invasive cases by menopausal status.

Talc use	All subjects				Premenopausal				Postmenopausal				Interaction
	Controls N=2099	Cases N=1540	OR (95% CI)[1]	p	Controls N=887	Cases N=516	OR (95% CI)[1]	p	Controls N=1212	Cases N=1023	OR (95% CI)[1]	p	p
Never	73.4%	66.2%	1.00		78.4%	72.5%	1.00		69.8%	63.0%	1.00		0.83
Ever	26.6%	33.8%	1.36 (1.17, 1.58)	<0.0001	21.6%	27.5%	1.21 (0.92, 1.59)	0.18	30.2%	37.0%	1.39 (1.16, 1.67)	0.0004	

Table 1C. Talc association in serous invasive cases by menopausal status.

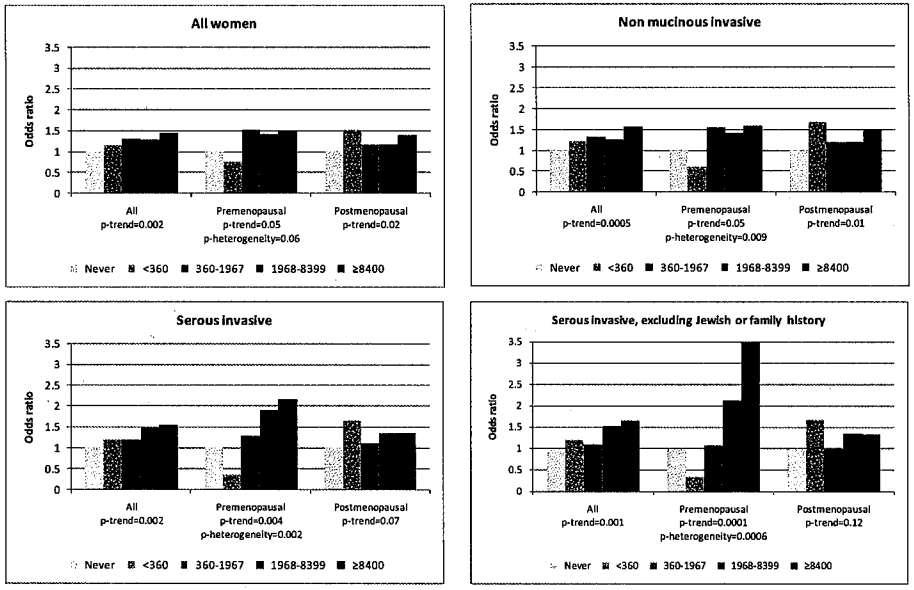
Talc use	All subjects				Premenopausal				Postmenopausal				Interaction
	Controls N=2099	Cases N=866	OR (95% CI)[1]	p	Controls N=887	Cases N=229	OR (95% CI)[1]	p	Controls N=1212	Cases N=637	OR (95% CI)[1]	p	p
Never	73.4%	65.2%	1.00		78.4%	71.2%	1.00		69.8%	63.1%	1.00		0.93
Ever	26.6%	34.8%	1.38 (1.15, 1.65)	0.0004	21.6%	28.8%	1.24 (0.86, 1.76)	0.24	30.2%	36.9%	1.38 (1.12, 1.70)	0.003	

Table 1D. Talc association in serous invasive cases by menopausal status, excluding women with Jewish ethnicity or family history of ovarian cancer or early onset breast cancer

Talc use	All subjects				Premenopausal				Postmenopausal				Interaction
	Controls N=1839	Cases N=686	OR (95% CI)[1]	p	Controls N=769	Cases N=173		p	Controls N=1070	Cases N=513	OR (95% CI)[1]	p	p
Never	73.3%	64.9%	1.00		77.9%	68.8%	1.00		70.0%	63.6%	1.00		0.66
Ever	26.7%	35.1%	1.39 (1.14, 1.69)	0.001	22.1%	31.2%	1.36 (0.91, 2.03)	0.13	30.0%	36.4%	1.35 (1.07, 1.70)	0.01	

[1]Adjusted for study phase and center, reference age, parity, OC use, tubal ligation, BMI, smoking, alcohol, Jewish ethnicity, and family history of ovarian or early onset breast cancer.

Figures 1A-D. Dose-response associations for total applications by menopausal status



Tables 1A through 1D and the corresponding figures demonstrate effects on the overall association and dose-response by systematically taking into consideration histologic type, menopausal status, and family history. The overall association of ovarian cancer with genital talc use [OR (and 95% CL)] was 1.30 (1.14, 1.49) for all cases, 1.36 (1.17, 1.58) for non-mucinous invasive cases, and 1.38 (1.15, 1.65) for invasive serous cases. For each of these groups, a dose-response based on control quartiles for total applications was present but only when the non-exposed group was included in the trend test. No significant interaction by menopausal status for ever-never use was observed, although the association was generally weaker in premenopausal women. The opposite was true for dose-response. Not only was the dose-response stronger in premenopausal compared to postmenopausal women, the interaction between menopausal status and dose-response was significant for non-mucinous invasive, invasive serous cases, and invasive serous cases unlikely to have been familial. In the latter group the dose response was especially striking. For invasive serous cancer unlikely to have had a familial origin, premenopausal women had odds ratios (and 95% limits) of 2.12 (1.16, 3.89) for about 2000 to 8400 applications and 3.53 (1.63, 7.65 for women with greater than 8400 applications, compared to women with no use. The p-trend for dose response was present whether non-exposed were included (p=0.001) or whether restricted only to talc users (p=0.001).

Conclusion

Taking into consideration histologic type of ovarian cancer leads to a marginal increase in the overall association between talc use and ovarian cancer. More importantly, menopausal status has a striking effect on the dose-response for the association. Premenopausal women, with frequent use may have more than a three-fold increase in their risk for invasive serous cancer of the ovary. Repeating these analyses in existing data sets may help clarify the association between talc and ovarian cancer.

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